

Spontaneous reporting—of what? Clinical concerns about drugs

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Background

Systematic spontaneous reporting of possible drug caused adverse effects began with the 'Yellow card system' in the UK in 1964. It was a medium for doctors to report their concerns on marketed drugs, thereby enhancing the limited premarketing clinical data on safety. Now 54 countries around the world have similar systems, and many warnings of adverse drug reactions and some deletions from the market have been made on the basis of such reports [1, 2].

There has been controversy about actions based on spontaneous reports. This relates to regulatory actions, thought by some to be disproportionate to an extremely small increased risk identified by a few spontaneous reports, or where causality has been thought to have been due to confounding and/or biases. Mostly, observational studies (case-control and cohort studies) have been the new 'gold standard' by which spontaneous reports are judged.

Recent papers have looked at some of the characteristics of spontaneous reporting systems, emphasizing the limitations [3–5]. The need to rejuvenate 'spontaneous reporting' systems of adverse reactions has been expressed, particularly in response to a fall in reporting rates in Britain [6]. So far few suggestions have been made in the published literature as to how it could be done.

This article looks again at what so-called 'spontaneous reports' are and what we can and should do with them.

Description and value, criticisms and limitations of 'spontaneous reports'

What is a spontaneous report?

'Spontaneous reports' are so-called because they arise during a clinician's normal diagnostic appraisal of a patient, the clinician drawing the conclusion that a drug may be implicated in the causality of the clinical event. As with all diagnoses the certainty of attribution will vary with the skill and experience of the doctor, what confirmatory tests may show, the natural history of the clinical event, and the existence of other plausible explanations.

Under-reporting, reports of known reactions, and false causality attribution are the common criticisms of spontaneous reporting systems [2–5]. However, several studies show that workload, doubt about causal relationship, and doubt about whether it is worth reporting, are the common reasons for under-reporting [7, 8].

It follows that the attribution of causality is at least as good as any other careful clinical diagnosis, often after the exclusion of other disease (because doctors are less likely to report where there is doubt over causality); if under-reporting is due to workload, then there must be a real motivation to send a report.

In a response to an open ended question [7] on why doctors report, the following were given as the main reasons, in order of frequency:

- motivation to contribute to medical knowledge;
- reaction previously unknown to reporter;
- reaction to new drug;
- all significant reactions reported;
- known association between drug and reaction;
- severity of reaction.

So, spontaneous reports are reports of genuine, general clinical concerns about a drug and suspected reaction. All must be treated as 'valid', in fact they should be labelled 'clinical concerns' rather than 'spontaneous reports' because the label is descriptively more explicit. Other reasons for reporting such as medico-legal considerations and current awareness of a particular drug problem were identified [7], but were of much less frequent concern to the international reporters surveyed.

Analysing and using report information

Reports of possible drug related events without having enough detail for a remote expert assessment constitute a well known problem, limiting the value of reports for some of the activities described below. This does not mean that the reported concern was invalid. In a previous article [9] we suggested that such reports, lacking in detail, should be considered as supporting evidence, but never disregarded. It is said that the numbers of reports do not indicate the frequency of an adverse reaction. This is true, but they *do* indicate the level of concern, which may, amongst other possibilities, indicate the frequency of a diagnosed reaction.

Reporting centre experts say they receive a lot of 'noise' from reports of known reactions which are of

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no importance. Because a reaction is known to pharmacologists/drug safety experts does not guarantee that it is fully communicated to clinicians. While the reports may not add anything new to knowledge about the drug, they may convey a very important message about how much prescribing physicians know about a given adverse reaction.

For understanding epidemiological issues

Case reports may be subject to 'bias' and 'confounding', but thoughtful analysis can identify this in most cases, and the knowledge can be useful. In an analysis of international reports of venous thrombo-embolism associated with oral contraceptives in the WHO database, there was a large increase in two countries of reports associated with the third generation drugs. This followed extensive press coverage of the issue. Interestingly the mortality rate in the cases during the time of increased reporting was much reduced, approximately four fold.

Diagnostic bias could have operated here in the way that clinicians were more alert and, with earlier diagnosis, management improved and mortality reduced. Other explanations are possible such as erroneous over-diagnosis of VTE, and dilution by increased reporting of less severe cases. Whatever the reason, this observation has important implications for our understanding of how publicity can influence medical practice for better or worse.

There has been far too great an emphasis placed on the view that bias can confuse the interpretation of reports or studies and not enough on the evaluation of what bias actually *means* and its possible impact on public health

For education

Physicians report because they wish to tell their colleagues of their experience. We should make sure that this happens: recurrent reports of common ADRs should be prompts for thinking about better communication/education on those ADRs. Some examples might be; the clinical expression of the adverse reaction (perhaps some reports were on unusually severe but common reactions); reports on special at risk groups (does poor elimination make some reactions more common/severe?); or reports suggesting interaction making the reaction more severe or more common.

The possibility of confounding of reported ADRs could be considered as a prompt for professional education, or the provision of diagnostic guidelines. It is worth here emphasizing that confounding means simply that another causation is possible. Without further knowledge, suggestions of confounding do not prove an

alternative causation. For example depression has been reported with Roaccutane use, but how much of this is due to psychological disturbance over the underlying severe acne in a sensitive teenager?

In this example is it possible to provide diagnostic hints if we can show or believe that both mechanisms operate? Prompts which might be helpful are:

presence/absence of pre-exposure depressive or other illness positive response to discontinuation of drug (How long is the drug effect likely to last?)

In terms of management:

advice on whether re-introduction of the drug is reasonable (Can we give advice on a time needed off treatment before re-introduction of drug?)

re-introduction at a lower dose (What dose recommendation can be given?)

specific treatment for the depression (Can the drug be safely continued and is there a risk of interactions?)

alternatives treatments for acne

This general approach to diagnosis and management regarding drugs and adverse reactions may be well known, but the questions included in parentheses are asking for key practical information to be given for this drug and ADR.

It is surprising that little help is offered on the diagnosis and management of adverse reactions, though the WHO Programme for International Drug Monitoring has just determined this as a topic for development at its last annual meeting of Programme members (Tokyo, September 1998). Perhaps, if we used the information from reported clinical concerns more imaginatively, as indicated in this section we would be able to reduce the burden of avoidable adverse reactions which may be about half the total [10, 11]. In particular we should see the reported clinical concern as a need for some response to the reporter and health professionals, not just in the context of its usefulness for new signal generation.

The concerns of others

It follows from the above that reports from patients and other health professionals must be regarded as *their* valid concerns, even though they may not be 'clinically validated'. What evidence there is suggests that patients and other health professionals report similar or even complementary issues with drugs. Pharmacists, nurses and dentists all make reports which have differing and important messages which reflect their special professional backgrounds and experiences. There is clear evidence of the success of pharmacists, for example, adding value to spontaneous reporting [12].

The reports from the different groups should be identified since their different concerns may need different

remedies. As an example, when the author was director of the national centre in New Zealand, at a time when there were about 10 reports of problems with copper IUCDs reported to the national centre, there were some 300 reports held by a consumer group. When the consumer reports were considered, this led to better training of doctors in insertion techniques. In Sweden a consumer group KILEN is very occupied with reports of benzodiazepine dependence, and antidepressant and analgesic use (conferences in Stockholm, Sweden, 1994; Reykjavik, Iceland, 1995; Mogenstrup, Denmark, 1997). This has resulted in general communications promoting short-term prescribing of benzodiazepines, amongst others. Such reports do not indicate new adverse reactions nor do they necessarily reflect a relatively large problem with the drugs. They are, however, important since they do reflect the need for appropriate action over the issues and general public guidance and education.

Having said that patients and other health professionals should be able to communicate their concerns to a recognized agency directly, ideally there is much to be gained by these groups reporting in collaboration with clinicians. Thus, the latter's clinical training and deeper medical knowledge of the patient can give added value to the report. It is also true that health professional reports should be made with the knowledge and collaboration of the patient, so that her/his views can be included.

Herxheimer (personal communication) proposed in 1983 for the UK, and repeatedly since, that patients should be informed when they are given a new drug, by putting the black triangle on the label, together with a card or a leaflet explaining that we all need to know more about the drug's effects, and that they can help by reporting anything unexpected to the doctor or pharmacist to be passed on to the central register. Involving the patient in this way is implicit in the Intensive Medicines Monitoring Programme (IMMP) in New Zealand [13], which has been in successful operation for about two decades producing useful signals and without drug scares.

Current regulatory reporting

Over recent years there have been major steps forward in developing regulated standard operating procedures for how the pharmaceutical industry and regulators should handle reports. The emphasis has been on the detection of new, serious suspected adverse reactions not noted in the product information. This work is the important traditional rôle of pharmacovigilance, but for many the load of completing these requirements on time, and to produce periodic safety updates, seems to have eclipsed more imaginative use of information.

The future

The problem with 'spontaneous reporting' starts with the trivializing appellation. These reports are clinical concerns, pharmacist concerns or patient/consumer concerns. What we do with them must bear those concerns in mind. We should not only be looking for new and rare adverse reactions, but also looking for opportunities to learn about the communities' concerns and general perceptions about drugs, and then to guide and educate. We should more frequently bring all the players involved in drug safety together, as has already been done once [14], to resolve misunderstandings, create trust and work together for improved public health.

Drug safety experts will say that they know all of the issue raised above; but their focus may be too inwardly directed. Findings from clinical concerns overall are infrequently communicated back along the lines, for example: "Doctors have reported to us most frequently this year on phenothiazine induced jaundice. Some deaths have occurred, all when higher doses and longer term prescriptions were used. We have identified certain 'at risk groups'....We can suggest early signs may be.... We can propose the following in the management....We can suggest alternative therapy....etc." It is a truism that better feed-back and reporter involvement leads to better reporting. In Australia, a questionnaire was used to ask doctors what they wanted from their system. Australia's reporting rate is one of the best in the world, based on the national figures held by the WHO Collaborating Centre for International Drug Monitoring.

A study in New Zealand showed that the use of specially designed prescription pads which prompted doctors to report on new drugs separately, increased the reporting rate 14-fold, and that was sustained. A feature of this method was that doctors only had to tick a box that an event had occurred; this took no time during their clinics. They were then given an easy-to-complete reminder [13]. A user friendly system can be provided in many ways, and is essential if we are to get reports from busy people. The same applies to getting maximal information: if we want it, reporters must know that it is valuable and it must be made as easy as possible to provide. Information technology may be useful.

Many of the respondents to our survey [7] on why doctors *had* reported adverse reactions offered reasons for why people did not report. One said that he felt that he was reporting to a 'bureaucratic black hole'. Information provided by clinicians must result in an output useful to them and more importantly to patients and consumers. Getting health professionals to feel involved and that they get useful feedback is essential. Regionalization such as introduced in France [15], improved the quantity and quality of reports to the WHO Programme. In France

there is a close association between drug information, poisoning information, and staff involved in clinical management of cases in many of the regional centres. Doctors in these regions know to whom they can turn for help. This can be contrasted with the intensive follow up of cases for ever more detail pursued by some pharmaceutical companies with the sole aim of fulfilling regulatory and medico-legal requirements. Provision of advice to the doctor is often proscribed by companies for medico-legal reasons.

Clinical concern and other reports serve public health in different ways. Let us find out how to make the most constructive use of them.

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